

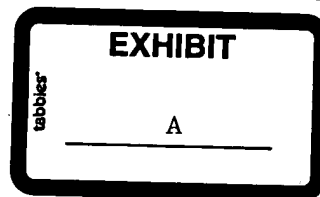
ADVANCED ORGANIC CHEMISTRY

REACTIONS,
MECHANISMS, AND
STRUCTURE

THIRD EDITION

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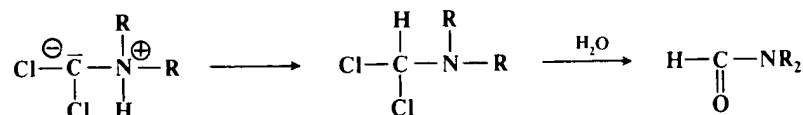
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The reaction can also be used synthetically for the preparation of isonitriles, though yields are generally not high.⁶⁸⁷ An improved procedure has been reported.⁶⁸⁸ When secondary amines are involved, the adduct cannot lose two moles of HCl. Instead it is hydrolyzed to an N,N-disubstituted formamide.⁶⁸⁹

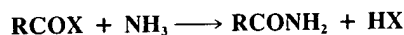


OS 55, 96.

B. Attack by NH₂, NHR, or NR₂ at an Acyl Carbon⁶⁹⁰

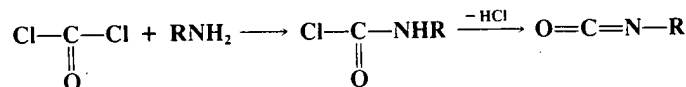
0-54 Acylation of Amines by Acyl Halides

Amino-de-halogenation

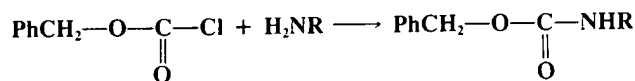


The treatment of acyl halides with ammonia or amines is a very general reaction for the preparation of amides.⁶⁹¹ The reaction is highly exothermic and must be carefully controlled, usually by cooling or dilution. Ammonia gives unsubstituted amides, primary amines give N-substituted amides, and secondary amines give N,N-disubstituted amides. Arylamines can be similarly acylated. In some cases aqueous alkali is added to combine with the liberated HCl. This is called the *Schotten-Baumann procedure* as in 0-22.

Hydrazine and hydroxylamine also react with acyl halides to give, respectively, hydrazides RCONHNH₂⁶⁹² and hydroxamic acids RCONHOH,^{692a} and these compounds are often made in this way. When phosgene is the acyl halide, both aliphatic and aromatic primary amines give chloroformamides ClCONHR that lose HCl to give isocyanates RNCO.⁶⁹³ This is one of the most common



methods for the preparation of isocyanates.⁶⁹⁴ Thiophosgene, similarly treated, gives isothiocyanates. A safer substitute for phosgene in this reaction is trichloromethyl chloroformate CCl₃OCOC_l.⁶⁹⁵ When chloroformates ROCOCl are treated with primary amines, carbamates ROCONHR' are obtained. An example of this reaction is the use of carbobenzoxy chloride to protect the amino group of amino acids and peptides:



⁶⁸⁷For a review of isonitriles, see Periasamy and Walborsky, *Org. Prep. Proced. Int.* **11**, 293-311 (1979).

⁶⁸⁸Weber and Gokel, *Tetrahedron Lett.* 1637 (1972); Weber, Gokel, and Ugi, *Angew. Chem. Int. Ed. Engl.* **11**, 530 (1972) [*Angew. Chem.* **84**, 587].

⁶⁸⁹Saunders and Murray, *Tetrahedron* **6**, 88 (1959); Frankel, Feuer, and Bank, *Tetrahedron Lett.* no. 7, 5 (1959).

⁶⁹⁰For a review, see Challis and Butler, in Patai, Ref. 309, pp. 279-290.

⁶⁹¹For review, see Beckwith, in Zabicky, Ref. 455, pp. 73-185.

⁶⁹²For a review of hydrazides, see Paulsen and Stoye, in Zabicky, Ref. 455, pp. 515-600.

^{692a}For an improved method, see Ando and Tsumaki, *Synth. Commun.* **13**, 1053 (1983).

⁶⁹³For reviews of the preparation and reactions of isocyanates and isothiocyanates, see, respectively, the articles by Richter and Ulrich, pp. 619-818, and Drobnica, Kristián, and Augustín, pp. 1003-1221, in Patai, "The Chemistry of Cyanates and Their Thio Derivatives," pt. 2, Wiley, New York, 1977.

⁶⁹⁴For examples, see Ozaki, *Chem. Rev.* **72**, 457-496 (1972), pp. 457-460. For a review of the industrial preparation of isocyanates by this reaction, see Twitchett, *Chem. Soc. Rev.* **3**, 209-230 (1974).

⁶⁹⁵Kurita and Iwakura, *Org. Synth.* **59**, 195.

Amino groups in general are often protected by conversion to amides. The treatment of acyl halides with lithium nitride gives N,N-diacyl amides (triacylamines).⁶⁹⁶

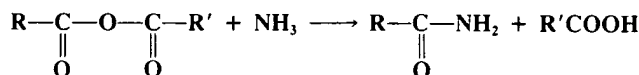


The reactions proceed by the tetrahedral mechanism.⁶⁹⁷

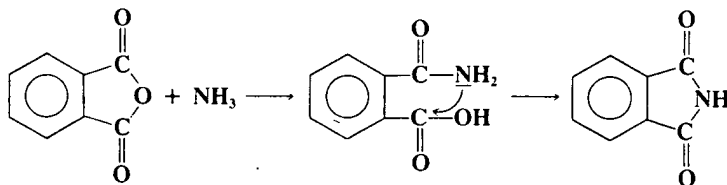
OS I, 99, 165; II, 76, 208, 278, 328, 453; III, 167, 375, 415, 488, 490, 613; IV, 339, 411, 521, 620, 780; V, 201, 336; 54, 88; 59, 195; 60, 72; 61, 17. See also OS 61, 71.

0-55 Acylation of Amines by Anhydrides

Amino-de-acyloxy-substitution



This reaction, similar in scope and mechanism to 0-54, can be carried out with ammonia or primary or secondary amines.⁶⁹⁸ However, ammonia and primary amines may also give imides, in which two acyl groups are attached to the nitrogen. This is especially easy with cyclic anhydrides, which produce cyclic imides.⁶⁹⁹



The second step in this case, which is much slower than the first, is the attack of the amide nitrogen on the carboxylic acid. Primary amines react with excess acetic anhydride to give N-alkyl or N-aryl imides, if magnesium is present to remove the acetic acid formed:⁷⁰⁰ $\text{RNH}_2 + \text{Ac}_2\text{O} + \text{Mg} \longrightarrow \text{RN}(\text{Ac})_2 + \text{Mg}(\text{OH})_2 + \text{H}_2$.

Even though formic anhydride is not a stable compound (see p. 487), amines can be formylated with the mixed anhydride of acetic and formic acids HCOOCOME ⁷⁰¹ or with a mixture of formic acid and acetic anhydride. Acetamides are not formed with these reagents. Secondary amines can be acylated in the presence of a primary amine by conversion to their salts and addition of 18-crown-6.⁷⁰² The crown ether complexes the primary ammonium salt, preventing its acylation, while the secondary ammonium salts, which do not fit easily into the cavity, are free to be acylated.

OS I, 457; II, 11; III, 151, 456, 661, 813; IV, 5, 42, 106, 657; V, 27, 373, 650, 944, 973; 56, 3.

0-56 Acylation of Amines by Acids

Amino-de-hydroxylation



When carboxylic acids are treated with ammonia or amines, salts are obtained. The salts of ammonia

⁶⁹⁶Baldwin, Blanchard, and Koenig, *J. Org. Chem.* **30**, 671 (1965).

⁶⁹⁷Kivinen, Ref. 413; Ref. 604, p. 185; Bender and Jones, *J. Org. Chem.* **27**, 3771 (1962).

⁶⁹⁸For a review, see Beckwith, in Zabicky, Ref. 455, pp. 86-96. For a review of peptide synthesis by treatment of an amino acid with a mixed anhydride of another amino acid, see Albertson, *Org. React.* **12**, 157-355 (1962).

⁶⁹⁹For reviews of imides, see Wheeler and Rosado, in Zabicky, Ref. 455, pp. 335-381; Hargreaves, Pritchard, and Dave, *Chem. Rev.* **70**, 439-469 (1970) (cyclic imides).

⁷⁰⁰Meyer, Nolde, Thomsen, and Lawesson, *Bull. Soc. Chim. Belg.* **87**, 621 (1978).

⁷⁰¹For the formylation of amines with the mixed anhydride of formic and trimethylacetic acid, see Vlietstra, Zwikker, Nolte, and Drenth, *Recl.: J. R. Neth. Chem. Soc.* **101**, 460 (1982).

⁷⁰²Barrett and Lana, *J. Chem. Soc., Chem. Commun.* 471 (1978).